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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUYNH, CARLIC K	
ART UNIT	PAPER NUMBER
1617	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/718,948	YING ET AL.	
	Examiner	Art Unit	
	Carlic K. Huynh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *6-8,11,22-30 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9,10,12-21 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to..

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *5 April 2007* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :28 February 2005 and 30 March 2005.

DETAILED ACTION

Status of the Claims

1. Claims 1-65 are pending in the application, with claims 33-65 having been cancelled, in response to the restriction requirement submitted on November 30, 2006. Accordingly, claims 1-32 are being examined on the merits herein.

Election/Restrictions

2. Applicant's election without traverse of Group I, namely claims 1-32, in the reply filed on January 30, 2007 is acknowledged.

3. Applicant's election without traverse of the species of (1) a reduction of β-adrenergic receptor mRNA levels as a pathological change, (2) albuterol as a β-adrenergic agonist, (3) asthma as a disease or condition, and (4) congestive heart failure as a heart disease, in the reply filed on January 30, 2007 is acknowledged.

The Examiner hereby withdraws the species of election requirement on (2) albuterol as a β-adrenergic agonist.

4. In a telephonic election of species requirement on April 5, 2007, Applicant's election of the species of (1) compound 215 (page 54 of the specification) as a small organic molecule is acknowledged. Applicants contend compound 215 reads on claim 32.

Claim 5 is read to draw on the elected species of a reduction in the mRNA level of a β-adrenergic receptor.

Claims 9-10 and 12-14 are read to draw on the elected species of asthma.

Claims 15-18 are read to draw on the elected species of congestive heart failure.

Claim 31 is read to draw on the elected species of compound 215.

Claims 6-8, 11, 22-30, and 32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on January 30, 2007.

The restriction requirement, the election of species requirement of (1) a reduction of β-adrenergic receptor mRNA levels as a pathological change, (3) asthma as a disease or condition, and (4) congestive heart failure as a heart disease, and the telephonic election of species of (1) compound 215 (page 54 of the specification) as a small organic molecule are still deemed proper and are therefore made FINAL.

Information Disclosure Statement

The Information Disclosure Statement submitted on February 28, 2005 and March 30, 2005 is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-16 and 19-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of a pathological change in the β-adrenergic signal transduction pathway in asthma and congestive heart failure does not reasonably provide

enablement for treatment of a pathological change in the β-adrenergic signal transduction pathway in any tissue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). ***Nature of the Invention***:

The rejected claim(s) is/are drawn to an invention which pertains to a method for counteracting a pathological change in the β-adrenergic signal transduction pathway.

(2). ***State of the Prior Art***:

The skilled artisan would view treatment of a pathological change in the β-adrenergic signal transduction pathway from any tissue as highly unlikely.

(3). ***Relative Skill of Those in the Art***:

The relative skill of those in the art of β-adrenergic signal transduction is extremely high.

(4). ***Predictability of the Art***:

Treatment of a pathological change in the β-adrenergic signal transduction pathway from any tissue is highly unpredictable. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and that physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Thus, the state of the art is highly unpredictable.

(5). ***Breadth of the Claims***:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass a method for counteracting a pathological change in the β-adrenergic signal transduction pathway.

(6). ***Direction or Guidance Presented***:

The guidance given by the specification as to a method for counteracting a pathological change in the β-adrenergic signal transduction pathway is limited.

The disclosure of a method for counteracting a pathological change in the β-adrenergic signal transduction pathway in lung and cardiac tissue is adequate (examples 1-3, pages 79-93).

(7). ***Working Examples***:

The working examples in the specification show experiments on the β-adrenergic signal transduction pathway from various tissue types. In example 1, the β-adrenergic signal transduction pathway from human bronchial smooth muscle cells and cardiomyocytes was studied (pages 79-84). In example 2, the β-adrenergic signal transduction pathway from cardiomyocytes was studied (pages 85-93). In example 3, the β-adrenergic signal transduction pathway from cardiomyocytes was studied (page 93). Thus, the working examples demonstrate examination of the β-adrenergic signal transduction pathway from human bronchial smooth muscle cells and cardiomyocytes but not for examination of the β-adrenergic signal transduction pathway from any tissue.

Note that lack of a working example for prevention is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.

(8). ***Quantity of Experimentation Necessary***:

The specification fails to provide sufficient support for examination of the β-adrenergic signal transduction pathway from any tissue. As a result, one of skill in the art would be forced to perform an exhaustive search for the embodiments of any phenolic antioxidant-chromium complex having the function recited in the instant claims suitable to practice the claimed invention.

Therefore, in view of the Wands factors, e.g. the predictability of the art, the amount of direction or guidence, and the lack of working examples discussed above, a person of skill in the art would not be able to fully practice the instant invention without ***undue experimentation***.

6. Claims 1-16 and 19-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compound 215 does not reasonably provide enablement for any β-adrenergic inhibitor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). ***Nature of the Invention***:

The rejected claim(s) is/are drawn to an invention which pertains to a method for counteracting a pathological change in the β-adrenergic signal transduction pathway with a β-

adrenergic inhibitor.

(2). ***State of the Prior Art***:

The skilled artisan would view treatment of a pathological change in the β-adrenergic signal transduction pathway with any β-adrenergic inhibitor as highly unlikely.

(3). ***Relative Skill of Those in the Art***:

The relative skill of those in the art of inhibitors of the β-adrenergic signal transduction pathway is extremely high.

(4). ***Predictability of the Art***:

Treatment of a pathological change in the β-adrenergic signal transduction pathway with β-adrenergic inhibitors is highly unpredictable. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and that physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Thus, the state of the art is highly unpredictable.

(5). ***Breadth of the Claims***:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass a method for counteracting a pathological change in the β-adrenergic signal transduction pathway with a β-adrenergic inhibitor.

(6). ***Direction or Guidance Presented***:

The guidance given by the specification as to a method for counteracting a pathological change in the β-adrenergic signal transduction pathway with a β-adrenergic inhibitor is limited.

The disclosure of a method for counteracting a pathological change in the β-adrenergic signal transduction pathway with compound 215 is adequate (examples 1-2, pages 79-93).

(7). ***Working Examples***:

The working examples in the specification show inhibition of the β-adrenergic signal transduction pathway with a β-adrenergic inhibitor. In examples 1 and 2, the β-adrenergic signal transduction pathway was inhibited using compound 215 (pages 79-93). Thus, the working examples demonstrate inhibition of the β-adrenergic signal transduction pathway using compound 215 but not for inhibition of the β-adrenergic signal transduction pathway using any β-adrenergic inhibitor.

Note that lack of a working example for prevention is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.

(8). ***Quantity of Experimentation Necessary***:

The specification fails to provide sufficient support for inhibition of the β-adrenergic signal transduction pathway with any β-adrenergic inhibitor. As a result, one of skill in the art would be forced to perform an exhaustive search for the embodiments of any phenolic

antioxidant-chromium complex having the function recited in the instant claims suitable to practice the claimed invention.

Therefore, in view of the Wands factors, e.g. the predictability of the art, the amount of direction or guidence, and the lack of working examples discussed above, a person of skill in the art would not be able to fully practice the instant invention without ***undue experimentation***.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-5, 9-10, 12-21, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Axon et al. (US 2004/0132730) in view of Li et al. (US 2004/0146509).

Axon et al. teach a method of treating various disorders associated with enhanced activity of transforming growth factor beta (TGFβ) and "enhanced activity" refers to any condition, wherein the effectiveness of TGFβ is undesirably high, regardless of the cause (page 1, paragraph [0002]; and page 2, paragraph [0028]). Thus the limitation of the pathological change of a reduction in the mRNA level of a β-adrenergic receptor as recited in instant claim 5 is met.

Axon et al. also teach the condition of congestive heart failure in humans as benefiting from their method (page 13, paragraphs [0063] and [0067]).

Axon et al. further teach compound 124 (page 43, Table 1), which is the same compound as the elected species of compound 215 in the instant application.

Axon et al. do not teach binding to TGFβ-R1 receptor kinase, asthma in humans as a condition, and binding to an additional kinase such as activin receptor (Alk4).

Li et al. teach a method for improvement of lung function by administering inhibitors of TGF-β specifically binding to the type I TGF-β receptor (TGFβ-R1) in a human subject (abstract; and page 1, paragraph [0009]). Li et al. further teach the disease or condition as asthma (page 1, paragraph [0011]).

Li et al. also teach other members of the superfamily of TGF-β include activin (page 1, paragraph [0005]). Since, the method of Li et al. disclose compounds that bind to TGF-β receptors and activin is a member of TGF-β superfamily, it is obvious that compounds that inhibit TGF-β receptors are capable of binding to other kinase such as activin receptor as recited in instant claims 19-20.

To a person of skill in the art at the time of the invention, it would have been obvious to employ the compounds of Axon et al. to inhibit TGFβ-R1 receptors and to treat asthma because the compounds of Li et al. inhibit TGFβ-R1 receptors and are used to treat asthma and according to Li et al., inhibition of TGFβ-R1 receptors is used to treat asthma.

The motivation to combine the compounds of Li et al. to the compounds of Axon et al. is that the compounds of Li et al. inhibit TGFβ-R1 receptors and that inhibition TGFβ-R1 receptors treat asthma.

Double Patenting

Obviousness-Type

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claim 1 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application Charkravarty et al. (US 2004/0038856), claim 1 of copending Application Higgins et al. (US 2004/0138188), claim 1 of copending Application Li et al. (US 2004/0146509), claims 1 and 24 of copending Application Medicherla et al. (US 2004/0192583), and claims 1 and 22 of copending Application Weller et al. (US 2005/0245508) in view of Axon et al. (US 2004/0132730) and Li et al. (US 2004/0146509) as applied to claims 1-5, 9-10, 12-21, and 31 above.

Charkravarty et al., Higgins et al., Li et al. (US 2004/0146509), Medicherla et al., and Weller et al. are all directed at a method of inhibiting TGF-β through the TGF-β receptor, TGFβ-R1. Each reference uses a specific compound to inhibit TGFβ-R1 receptor. Each reference is

rendered obvious over the instant application because the instant application employs "a compound" to inhibit the TGF-β receptor.

This is a provisional double patenting rejection since the conflicting claims have not been patented.

Conclusion

8. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carlic K. Huynh whose telephone number is 571-272-5574. The examiner can normally be reached on Monday to Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ckh